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Risk Factors for the Incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS)

AREDS Report No. 19

Age-Related Eye Disease Study Research Group*

Abstract

Purpose: To describe the association of demographic, behavioral, medical, and nonretinal ocular factors with the incidence of neovascular age-related macular degeneration (AMD) and central geographic atrophy (CGA) in the Age-Related Eye Disease Study (AREDS), a randomized trial of antioxidants and zinc supplementation prophylaxis for development of advanced AMD.

Design: Clinic-based prospective cohort study.

Participants: Of individuals with early or intermediate AMD at baseline with a median follow-up of 6.3 years, 788 were at risk of developing advanced AMD in one eye (the fellow eye had advanced AMD), and 2506 were at risk in both eyes.

Methods: The incidence of neovascular AMD and CGA was assessed from stereoscopic color fundus photographs taken at baseline and at annual visits beginning at year 2.

Main Outcome Measures: Neovascular AMD was defined as photocoagulation for choroidal neovascularization, or photographic documentation at the reading center of any of the following: nondrusenoid retinal pigment epithelial detachment, serous or hemorrhagic retinal detachment, hemorrhage under the retina or the retinal pigment epithelium, and subretinal fibrosis. Central geographic atrophy was defined as geographic atrophy involving the center of the macula.

Results: In multivariable models, in persons at risk of advanced AMD in both eyes, while controlling for age, gender, and AREDS treatment group, the following variables were statistically significantly associated with the incidence of neovascular AMD: race (odds ratio [OR], white vs. black, 6.77; 95% confidence interval [CI], 1.24-36.9) and larger amount smoked (OR, >10 vs. ≤10 pack-years [a pack-year is an average of 1 pack of cigarette smoked per day for a year], 1.55; 95% CI, 1.15-2.09). The following were statistically significantly associated with the incidence of CGA: less education (OR, high school graduate or less vs. college graduate, 1.75; 95% CI, 1.10-2.78), greater body mass index (BMI) (OR, obese vs. nonobese, 1.93; 95% CI, 1.25-2.65), larger amount smoked (OR, >10 pack-years vs. ≤10 pack-years, 1.82; 95% CI, 1.25-2.65), and antacid use (OR, 0.29; 95% CI, 0.09-0.91). In persons at risk of developing advanced AMD in one eye, the incidence of neovascular AMD was associated with diabetes (OR, 1.88; 95% CI, 1.07-3.31), and the incidence of CGA was associated with use of antiinflammatory medications (OR, 0.22; 95% CI, 0.08-0.59).

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Conclusions: Results suggest that, among persons with early or intermediate AMD, smoking and BMI are modifiable factors associated with progression to advanced AMD, and suggest other associations (e.g., use of antacids and antiinflammatory medications) that warrant further study.

There are approximately 8 million persons in the United States over the age of 55 years with features of early or intermediate age-related macular degeneration (AMD) who are at high risk of developing advanced AMD and experiencing at least moderate visual loss, of whom approximately 1 million will develop advanced AMD within the next 5 years.[1] Despite the magnitude of this problem, few factors have been identified that alter the course of the disease once signs of early or intermediate AMD are present.[2,3] Most notably, the Age-Related Eye Disease Study (AREDS) in a randomized controlled clinical trial showed that an antioxidant vitamin/mineral supplement delayed the progression from intermediate to advanced disease by 25% over 5 years.[4] These results have altered the management of patients with this common condition. Cigarette smoking, the most consistent risk factor for onset of the disease,[2,3,5-9] and, less consistently, blood pressure (BP),[2,3,7,9,10] pulse pressure,[8,10,11] lipid levels,[2,3,10,11] abdominal obesity,[2,3,12] physical activity,[2,3,10,12] dietary fat,[13-15] and cataract surgery[2,16,17] have been associated with development and progression of AMD. The purpose of this report is to evaluate the associations of demographic, behavioral, medical, and nonretinal ocular risk factors measured at baseline with development of neovascular AMD and central geographic atrophy (GA) among patients with early or intermediate AMD in the AREDS.

Materials and Methods

Study Population

Details of the study design and methods, presented elsewhere,[18] are briefly summarized here. Eleven retinal specialty clinics enrolled 4757 participants in the AREDS from 1992 through 1998. Participants were 55 to 80 years old at enrollment and had best-corrected visual acuity (BCVA) of 20/32 or better in at least one eye (the study eye[s]). Media had to be sufficiently clear to obtain adequate quality stereoscopic fundus photographs of the macula in all study eyes. Visual acuity (VA) was assessed by certified examiners using the Early Treatment Diabetic Retinopathy Study logarithm of the minimum angle of resolution chart and a standardized refraction and VA protocol.[19] Persons were enrolled in 1 of 4 AMD categories determined by the presence, size, and extent of drusen and retinal pigment epithelial abnormalities in each eye, the presence of advanced AMD (each determined by evaluation of stereoscopic color photographs at a reading center), and VA. Informed consent was obtained from all AREDS participants, and institutional review board approval was obtained by the clinics.

Briefly, persons in category 1 were essentially free of age-related macular abnormalities, with a total drusen area of <5 small drusen (<63 μm in diameter), and had VA of 20/32 or better in both eyes. Category 2 participants had mild or borderline age-related macular lesions (multiple small drusen, nonextensive [<20] intermediate drusen [63-124 μm in diameter], pigment abnormalities, or any combination of these) in their most advanced eye and VA of 20/32 or better in both eyes. Category 3 required absence of advanced AMD in both eyes and at least 1 eye with VA of 20/32 or better, with at least 1 large druse (≥125 μm in diameter), extensive (as measured by drusen area) intermediate drusen, GA that did not involve the center of the macula, or any combination of these. In category 3a, both eyes met these criteria, whereas in category 3b one eye had either reduced VA not due to AMD or a disqualifying ocular condition. Category 4 participants had VA of 20/32 or better and no advanced AMD (GA involving the center of the macula or features of choroidal neovascularization) in the study eye, and the fellow eye had either lesions of advanced AMD (category 4a) or VA less than 20/32 and AMD abnormalities sufficient to explain reduced VA (category 4b), as determined by examination

of photographs at the reading center. Persons 55 to 59 years old were eligible for the study only if they were in category 3 or 4.

The assessment of risk factors for progression to advanced AMD is restricted in this report to participants in categories 2 and 3a, and separately to participants in category 4a. Category 1 participants were excluded from the analyses because progression to advanced AMD was rare (<1%) for this group.[4] Categories 2 and 3a participants (defined as the bilateral drusen group; n = 2506) had varying degrees of drusen and pigmentary abnormalities in both eyes and the ability to progress to advanced AMD in both eyes. Category 3b participants (n = 156) were excluded from these analyses because not all eyes in this group could be evaluated for these characteristics. Participants in category 4a (unilateral advanced AMD; n = 788) were analyzed separately from those in categories 2 and 3a because patients in category 4a are at notably higher risk of progression, and each of these participants had only one eye that could progress.[20,21] Participants in category 4b (n = 159) were not analyzed with the 4a participants because they did not have unilateral advanced AMD and therefore had a different risk of progression. They also differed enough from the categories 2 and 3a participants that it seemed inappropriate to include them in a combined analysis.

Procedures

Detailed questionnaires were administered to obtain demographic information, history of smoking and sunlight exposure, medical history, history of specific prescription drug and nonprescription medication use, and history of vitamin and mineral use. General physical and ophthalmic examinations included height, weight, BP, manifest refraction, BCVA, intraocular pressure, slit-lamp biomicroscopy, and ophthalmoscopy. Slit-lamp photographs and Neitz photographs of the lens were taken along with stereoscopic fundus photographs of the macula and red reflex lens photographs. These were graded at a photograph reading center, where the various lesions associated with AMD and the degree of lens opacities by type were assessed through standardized grading procedures.[17,18]

Outcomes

Progression to neovascular AMD for a study eye was based on clinical center reports of photocoagulation for choroidal neovascularization or photographic documentation at the reading center of any of the following: nondrusenoid retinal pigment epithelial detachment, serous or hemorrhagic retinal detachment, hemorrhage under the retina or the retinal pigment epithelium (RPE), and/or subretinal fibrosis. The analysis of progression to central GA (GA definitely involving the center of the macula, or questionably involving the center but definitely present proximally, based on reading center reports) did not count central GA when occurring in an eye exhibiting subretinal fibrosis at the same visit. With this one exception, analyses of progression to either neovascular AMD or central GA are without regard to progression to the other. Analyses involve progression within a participant, regardless of whether one or two eyes progressed.

Risk Factor Definitions

We evaluated risk factors for progression to advanced AMD, separately for neovascular AMD and central GA. The baseline risk factor variables are divided into 4 classes: demographic and behavioral, medical history, use of medications, and ocular (nonretinal). For analysis, continuous variables were categorized into 3 groups by the first and last quintiles, except for age in years, which had categories 55 to 64, 65 to 69, and 70 to 80, and body mass index (BMI), which had categories <18.5, 18.5 to 24.9, 25.0 to 29.9, and ≥30 kg/m^2 (underweight, normal, overweight, and obese, respectively), as defined by the National Heart, Lung, and Blood Institute and the World Health Organization.[22]

Demographic and Behavioral. The demographic and behavioral variables included age, race, gender, education, history of smoking, BMI, weight change since age 20, and sunlight exposure (adult lifetime average annual ocular ultraviolet B exposure, adapted from McCarty et al[23]).

Medical History. Medical history variables included uncontrolled hypertension (systolic > 160 mmHg and/or diastolic > 90 mmHg, either untreated or treated); controlled hypertension (systolic ≤ 160 mmHg and diastolic ≤ 90 mmHg and currently using antihypertensive medication); no hypertension (systolic ≤ 160 mmHg and diastolic ≤ 90 mmHg and not using antihypertensive medication); pulse pressure (an indirect measure of arterial stiffness, defined as the difference between systolic and diastolic BPs); and history of angina, diabetes (under treatment for diabetes by diet, oral hypoglycemic agent, and/or insulin), skin cancer (melanoma, basal or squamous cell), or arthritis.

Use of Medication. Any medication that was used at the time of the baseline examination and was regularly used for at least 5 years by at least 5% of participants was considered for analysis as a risk factor. The following medications qualified for analysis: diuretics (other than hydrochlorothiazide), hydrochlorothiazide, β-blockers, calcium channel blockers, aspirin, antacids, nonsteroidal antiinflammatory drugs, thyroid hormones, and estrogen and progesterone (women). The AREDS treatment was randomly assigned in the clinical trial: daily oral supplements with antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg) alone, zinc (zinc, 80 mg; copper, 2 mg) alone, antioxidants plus zinc, or a placebo.[4]

Ocular (Nonretinal). Ocular variables included iris color, refractive error, and lens opacity. Iris color was graded by the reading center by comparing iris photographs of each eye with standard photographs depicting a scale from 1 (light or blue) to 4 (dark or brown); a person′s iris color was considered to be light if both eyes were code 1, dark if both eyes were code 4, and mixed if otherwise.

A person was considered myopic if both eyes had a refractive error of -1.0-diopter (D) spherical equivalent (SE) or more, hyperopic if both eyes had +1.0-D SE refractive error or more, or other, which included emmetropia and mixed cases. Persons with bilateral aphakia (n = 106) were excluded from analyses involving refractive error. The refractive error of the phakic eye was used to classify the refractive status of participants with unilateral pseudophakia. A person was categorized as having a lens opacity or cataract if at least one eye had an opacity of any type (a nuclear opacity grade of ≥4, a cortical opacity involving ≥6% of the central 5-mm circle, or a posterior subcapsular opacity involving ≥1% of the central 5-mm circle) or had a history of cataract surgery.[24]

Statistical Modeling and Analyses

Risk factors were identified in a 2-stage process using repeated-measures logistic regression (Procedure GENMOD[25]), a generalized estimating equations method that allows for determining outcomes at each visit for each participant.[26] The 2 stages were performed for each of the 4 outcome-participant combinations (2 outcomes: incident neovascular AMD and central GA; 2 AMD category groups: bilateral drusen and unilateral advanced AMD). In stage 1, each risk factor was included separately in a univariable analysis adjusted for age, gender, and AREDS treatment. Variables identified as significant (P<0.15) for progression to an outcome were retained as risk factors for further analysis. Multilevel categorical variables were retained if the high versus low (top 20% vs. bottom 20%) comparison was significant.

In stage 2, all variables retained from stage 1 from any of the regressions were entered as a group into a single multivariable repeated-measures logistic regression, and then model simplification consistent with chi-square tests of change in deviance was performed. This simplification consisted of identifying nominally nonsignificant (P>0.1) coefficients from

stage 2 and removing those variables from the model. Model simplification continued until the reduced model yielded a significant (P<0.05) worsening of fit according to the likelihood ratio criterion. The significance of hormone use among women was evaluated by including it in the final model restricted to women. Odds ratios (ORs) and 95% confidence intervals (CIs), which describe the association between progression and the risk factors, were computed for each variable.

Results

In Table 1, baseline risk factors are categorized for the bilateral drusen participants and the participants with unilateral advanced AMD. For the 2506 participants in the bilateral drusen group, the mean age was 68.5 years (standard deviation [SD], 5.0). For the 788 participants with unilateral advanced AMD, the mean age was 70.3 years (SD, 5.2). Mean follow-up time for all participants was 6.3 years. More females than males participated, and they were predominantly (96%-98%) white. Relative to the bilateral drusen group, the subjects with advanced AMD tended to be older, have fewer years of formal education, smoke more, have higher BMI, have higher BP, be myopic, have a history of angina (not shown), be more likely to have a lens opacity, and be less likely to take hormones (women).

Incident Neovascular Age-Related Macular Degeneration

Of the 2506 participants in the bilateral drusen group, 256 (10%) developed neovascular AMD in at least one eye during the course of the study. Of the 788 participants in the unilateral advanced AMD group (n = 714 with neovascular AMD in their nonstudy eye at baseline), 278 (35%) developed a neovascular outcome.

In stage 1 analyses (as shown in online-only Table 2, available at http://www.ophsource.org/periodicals/ophtha), for participants in the bilateral drusen group, controlling for age, gender, and trial treatment assignment, the following variables were each nominally associated (P<0.15) with increased odds of progression to neovascular AMD: white race, smoking more than 10 pack-years (a pack-year is an average of 1 pack of cigarettes smoked per day for a year), history of angina, antacid use, and calcium channel-blocker use. In stage 2 analyses (Table 3), in which all variables nominally significant in stage 1 analyses were entered in a similarly controlled multivariable regression, white race and smoking more than 10 pack-years were independently associated with incident neovascular AMD. Antacid use was borderline significant.

Similar staged analyses done for the participants with unilateral advanced AMD (online-only Table 2, available at http://www.ophsource.org/periodicals/ophtha; Table 3) found that presence of diabetes mellitus increased risk.

Central Geographic Atrophy

Central GA developed during the course of the study in 140 (6%) of the 2506 bilateral drusen group participants and in 83 (10%) of the 788 participants in the unilateral advanced AMD group (n = 74 with central GA in their nonstudy eye at baseline).

In stage 1 analyses (online-only Table 2, available at http://www.ophsource.org/periodicals/ophtha), while controlling for age, gender, and treatment, the following variables were nominally associated with developing central GA in persons in the bilateral drusen group: fewer years of formal education, history of angina, smoking more than 10 pack-years of cigarettes, being obese, an increase in body weight between age 20 and the baseline examination, use of calcium channel blockers or β-blockers, not using antacids, not using hormone replacement (women), and having lighter iris color. In stage 2 analyses of the bilateral drusen group (Table

3), the following variables were independently associated with incident central GA: fewer years of formal education, being obese, smoking more than 10 pack-years, and not using antacids.

Similar staged analyses were done for persons with unilateral advanced AMD (online-only Table 2, available at http://www.ophsource.org/periodicals/ophtha; Table 3). The risk was lower for persons using antiinflammatory drugs (OR, 0.22; 95% CI, 0.08-0.59).

Discussion

Results of these analyses provide information regarding associations of demographic, behavioral, medical, and nonAMD ocular factors with the incidence of neovascular AMD and central GA among participants with preexisting signs of AMD. Strengths include the standardized protocols for obtaining data, standardized definitions for risk exposure, photographic assessment of the outcomes and retinal risk categories, the large size of the cohort (n = 3394) at risk for these conditions, and the relatively large number of outcomes (534 for neovascular AMD and 223 for central GA).[4,9,18,20,24] Most of the AREDS risk factors for incident AMD are similar to those found in other studies.

In the AREDS, individuals with more pack-years of smoking had an increased risk of incident neovascular AMD and central GA. This is consistent with data from most but not all earlier studies.[5-9,27-29] Cigarette smoke may affect macular luteal pigment, and it increases oxidative stress and impairs the choroidal microcirculation, all mechanisms hypothesized to be involved in the pathogenesis of AMD.[30-33]Although these epidemiologic data do not provide definitive evidence that stopping smoking prevents the development of advanced AMD, patients should be advised not to smoke because of the significant known adverse affects of smoking on health.[34]

The lower incidence of neovascular AMD in blacks compared with whites in the AREDS is consistent with data from anecdotal observations that loss of vision due to choroidal neovascularization is rarely seen in blacks attending specialty eye clinics and from most population-based studies.[2,3,9,35-40]Choroidal melanin has been hypothesized to have a protective effect on the RPE, photoreceptors, and Bruch′s membrane, perhaps through an antioxidant effect or an ability to absorb light rays that damage the posterior layers of the retina.[41] However, in most of these studies that included both whites and blacks, there were too few blacks with neovascular AMD to examine the reason for these racial differences. Although the incidence of neovascular AMD in blacks is lower, it is not negligible. Data from one recent study, the Salisbury Eye Evaluation, showed that the prevalence of choroidal neovascularization was 1.1% in blacks, compared with 1.7% in whites (Bressler SB et al, unpublished data). Ophthalmologists should be alert to the possibility of this condition as a reason for visual loss in blacks.

Greater body mass was found to be associated with higher risk of incident GA in our study. The only other study that specifically evaluated progression from early or intermediate AMD to advanced AMD also demonstrated an increased risk with higher BMI.[12] That study also found an association between progression of AMD and waist-hip ratio and waist circumference as measures of abdominal adiposity. Because the AREDS did not collect similar information, we were unable to confirm these results. Cross-sectional data from the Finnish Oulu study suggested a relationship with greater body mass, and these investigators speculated that, if not a chance finding, it may be a result of excessive caloric intake that increased the risk of AMD because of an increased risk of oxidative damage.[42] Obesity may also be a marker of reduced physical activity, which was also found to be related to progression of AMD and has been shown to be related to a higher risk of neovascular AMD, but not incident GA.[10,12] It may also be associated with an increase in inflammation, a postulated pathogenic factor for AMD.[43,44] Other studies have not found such a relationship of obesity with incident AMD, whereas

still others have reported an association of lean body mass with increased risk of GA, an association not found in the AREDS.[2,7,10,45]

Once age and treatment assignment were controlled for, many of the factors under study (e.g., systemic hypertension, angina, sun exposure, cataract status, refractive error, iris color) were no longer statistically significantly associated with incident neovascular AMD or GA. However, there were a number of borderline or weak associations found between other factors, such as presence of diabetes, use of nonsteroidal antiinflammatory agents, and hormone replacement therapy, and the incidence of either GA or neovascular AMD that have been inconsistently reported in other studies.[2,3,7,28,46-51]The inconsistency among studies may also be due in part to different genetic admixtures or to differences in ascertainment or participation. For example, there were 181 participants in the AREDS bilateral drusen group who also had diabetes. Of these, only 16 developed neovascular AMD and 6 developed central GA during the course of the study. With few incident cases, the power to test for statistically significant associations is weak, unless the relative risk is very high. In this case, relative risks would have to be >2.3 and >5.2, respectively, to have 85% power to find a statistically significant association ($P<0.05$). Failure to find associations may also be due to the insensitivity of some of the risk factor measurements (e.g., sunlight exposure) or due to selective survival. Conversely, some of the relations we report may be due to chance, bias, and unadjusted confounding. We have studied a large number of possible risk factors and conducted multiple tests of significance. Therefore, some of our significant findings may be due to chance. This may be a particularly important consideration for those variables that have not been found to be associated with the development of advanced AMD in other studies, such as our finding of a decreased risk of developing neovascular ARM in those taking antacids at baseline and an increased risk of developing GA in those taking calcium channel blockers. We note that significant risk factors for incidence of advanced AMD in this study (education, smoking, race, age, and BMI) were also significant in the earlier AREDS report on prevalence of AMD.[9]

In this report, we have focused on nonretinal risk factors. As expected, early signs of disease are strong predictors of subsequent advanced disease: drusen area (or drusen size), RPE depigmentation, and increased pigment. When these baseline retinal risk factors are included in our multivariable analyses, there is minimal impact on the magnitude of estimates of ORs for the nonretinal factors, but CIs may be widened and statistical significance may exceed levels traditionally considered significant (data not shown). Thus, the nonretinal factors identified as possibly important by the unadjusted analyses remain identified but with less precision after adjusting for the retinal factors.

In summary, these AREDS results demonstrate a relationship between smoking at baseline and development of advanced AMD among individuals with preexisting AMD. Results also confirm the association with BMI and provide new insights regarding other factors (e.g., use of antacids and anti-inflammatory medications) that require further study.

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Table 1

Baseline Characteristics

	Bilateral Drusen(N 2506) [N (%)]	Unilateral Advanced AMD (N 788) [N (%)]
AMD category		
2	1053 (42)	
3a	1453 (58)	
4a		
Neovascular AMD		714
Central GA		74
AREDS treatment		
Antioxidants	633 (25)	211 (27)
Zinc	633 (25)	197 (25)
Antioxidants + zinc	609 (24)	192 (24)
Placebo	631 (25)	188 (24)
Demographic and behavioral		
Age (yrs)		
<65	548 (22)	122(15)
65-69	888 (35)	198 (25)
≥70	1070 (43)	468 (59)
Gender		
Male	1057 (42)	365 (46)
Female	1449 (58)	423 (54)
Education		
High school or less	859 (34)	367 (47)
Some college	755 (30)	229 (29)
College graduate	890 (36)	192 (24)
Race		
White	2398 (96)	775 (98)
Other	108 (4)	13 (2)
Smoking		
≤10 pack-years	1544 (62)	355 (45)
>10 pack-years	962 (38)	433 (55)
Body mass index		
Underweight(<18.5)	24 (1)	7 (1)
Normal (18.5-24.9)	833 (33)	214 (27)
Overweight (25-29.9)	1048 (42)	324 (41)
Obese (≥ 30)	600 (24)	243 (31)
Weight change since age 20		
Bottom 20%	529 (21)	153 (19)
Middle 60%	1451 (58)	433 (55)
Top 20%	522 (21)	202 (26)
Medical history		
Hypertension		
Normal	1543 (62)	420 (53)
Controlled	599 (24)	225 (29)
Uncontrolled	173 (7)	67 (8)
Untreated	191 (8)	76 (10)
Angina		
Absent	2281 (91)	679 (86)
Present	225 (9)	109 (14)
Diabetes		
Absent	2325 (93)	716 (91)
Present	181 (7)	72 (9)
Use of medication		
Aspirin		
Absent	2233 (89)	702 (89)
Present	273 (11)	86 (11)
Antacids		
Absent	2375 (95)	740 (94)
Present	131 (5)	48 (6)
Antiinflammatory drugs		
Absent	2204 (88)	687 (87)
Present	302 (12)	101 (13)
Calcium channel blockers		
Absent	2397 (96)	734 (94)
Present	101 (4)	49 (6)
Hormones (women)		
Absent	611 (42)	218 (52)
Present	830 (58)	199 (48)
Ocular		
Lens opacity		
Absent	1507 (60)	386 (49)
Present	999 (40)	402 (51)
Iris color		

	Bilateral Drusen(N 2506) [N (%)]	Unilateral Advanced AMD (N 788) [N (%)]
Light	544 (22)	154 (20)
Mixed	1734 (69)	566 (72)
Dark	227 (9)	65 (8)
Refractive error		
Myopic	354 (14)	63 (9)
Mixed	1060 (43)	322 (43)
Hyperopic	1034 (42)	355 (48)

AMD= age-related macular degeneration; AREDS=Age-Related Eye Disease Study; GA=geographic atrophy;pack-year=average of 1 pack of cigarettes smoked per day for a year.

Table 2

Age-, Gender-, and AMD Treatment-Adjusted Associations (Odds Ratios) between Progression to AMD (Neovascular and Central GA) and Baseline Risk Factors.

	Exposure			Bilateral Drusen		Unilateral Advanced AMD	
Factors	**A**	**vs.**	**B**	**Neovascular**	**Central GA**	**Neovascular**	**Central GA**
Age (yrs)	65-69		<65	1.74	1.68	1.62	1.28
	>70		<65	2.43	2.00	1.92	1.49
Gender	Male		Female	0.93	1.10	0.75	1.15
AREDS treatment	Antioxidants		Placebo	0.71	0.77	0.69	1.01
	Zinc		Placebo	0.87	0.82	0.56	0.81
	Antioxidants + zinc		Placebo	0.84	0.71	0.41	1.83
Education	College graduate		High school or less	1.15	0.55	0.79	1.36
Race	White		Other	7.07	3.97	1.73	-
Smoking (pack-years)	>10		≤10	1.58	1.79	1.09	0.72
Body mass index	Underweight		Normal	0.85		0.70	
	Overweight	Normal		1.03		1.19	
	Overweight		Normal/ underweight		1.56		1.36
	Obese		Normal	1.15		1.15	
	Obese		Normal/ underweight		2.00		1.43
Weight change	Top 20%		Bottom 20%	1.26	2.17	1.36	1.89
Sun exposure	Top 20%		Bottom 20%	1.02	1.04	0.72	0.59
Pulse pressure	Top 20%		Bottom 20%	0.79	1.09	1.27	1.80
Hypertension	Controlled		Normal	0.98	0.92	1.01	1.44
	Uncontrolled		Normal	0.85	0.86	0.73	0.33
	Untreated		Normal	1.12	0.82	1.27	1.34
Angina	Present		Absent	1.60	1.54	0.83	0.63
Diabetes	Present		Absent	1.08	0.62	1.69	0.56
Skin cancer	Present		Absent	1.42	1.43	0.82	1.42
Arthritis	Present		Absent	1.09	0.99	1.01	1.32
Diuretic use	Present		Absent	0.99	1.07	0.74	1.19
Aspirin use	Present		Absent	1.30	1.00	1.12	0.25
Antacid use	Present		Absent	1.80	0.33	1.16	0.77
Hydrochlorothiazide use	Present		Absent	0.80	1.22	1.00	1.02
Antiinflammatory drugs	Present		Absent	0.94	1.14	0.99	0.23
Thyroid hormones	Present		Absent	0.86	1.16	1.39	0.88
β-blocker use	Present		Absent	0.70	1.71	0.64	0.93
Calcium channel-blocker use blocker use	Present		Absent	1.86	2.22	1.11	0.38
Hormone use (women)	Present		Absent	1.20	0.60	1.03	1.03
Lens opacity	Present		Absent	1.02	1.03	1.07	0.96
Iris color	Dark		Light	0.78	0.49	1.30	0.22
Refractive error	Hyperopic		Myopic	1.11	1.31	1.71	0.70

AMD = age-related macular degeneration;AREDS,Age-Related Eye Disease Study;GA = geographicatrophy; pack-year=average of 1 pack of cigarettes smoked per day for a year. Boldface odds ratios are nominally significant (P <0.15)

Table 3

Odds Ratios (95% Confidence Intervals) for the Final Model (Nonsignificant Variables Omitted)

Factors	Exposure			Bilateral Drusen		Unilateral Advanced AMD	
	A	vs.	B	Neovascular	Central GA	Neovascular	Central GA
Age (yrs)	65-69		<65	1.67(1.05-2.67)*	1.67 (0.97-2.89)	1.65 (1.00-2.72)*	1.26 (0.55-2.91)
	>70		<65	2.37(1.52-3.71)†	2.05 (1.23-3.43)†	1.94(1.24-3.04)†	1.66 (0.80-3.44)
Gender	Male		Female	0.83 (0.61-1.14)	0.96 (0.65-1.42)	0.70 (0.51-0.96)*	1.18 (0.72-1.93)
AREDS treatment	Antioxidants		Placebo	0.72 (0.47-1.09)	0.78 (0.47-1.31)	0.73 (0.48-1.11)	1.04 (0.51-2.13)
	Zinc		Placebo	0.85 (0.57-1.28)	0.80 (0.49-1.31)	0.53 (0.35-0.81)†	0.76 (0.35-1.65)
	Antioxidants zinc		Placebo	0.83 (0.55-1.25)	0.69 (0.41-1.16)	0.39 (0.25-0.59)†	1.87 (0.96-3.66)
Education	College graduate		High school or less		0.57 (0.36-0.91)*		
Race	White		Other	6.77 (1.24-36.90)*			
Body mass index	Underweight		Normal				
	Overweight		Normal				
	Overweight		Normal/ underweight		1.51 (0.94-2.42)		
	Obese		Normal				
	Obese		Normal/ underweight		1.93(1.16-3.21)*		
Smoking	>10 pack-years		≤10 pack-years	1.55 (1.15-2.09)†	1.82 (1.25-2.65)†		
Hypertension	Controlled		Normal				
	Uncontrolled		Normal				
	Untreated		Normal				
Weight change		Top 20%	Bottom 20%			1.99 (0.87-4.59)	
Sun exposure	Top 20%		Bottom 20%				
Angina	Present		Absent				
Diabetes	Present		Absent			1.88(1.07-3.31)*	
Aspirin use	Present		Absent				
Antacid use	Present		Absent	1.70 (0.99-2.95)	0.29 (0.9-0.91)*		
Antiinflammatory drug use	Present		Absent				0.22 (0.08-0.59)†
Calcium channel blocker use	Present		Absent				
Iriscolor	Dark		Light		0.44 (0.19-1.02)		
Hormone use (women)	Present		Absent		0.65 (0.40-1.06)		
Lens opacity	Present		Absent				
Refractive error	Hyperopic		Myopic			1.70 (0.89-3.25)	

AMD age-related macular degeneration; AREDS Age-Related Eye Disease Study; GA geographic atrophy; pack-year average of 1 pack of cigarettes smoked per day for a year.

*P≤0.05.

†P ≤0.01.